Q91 July 20, 1958

Biopoiesis

We believe that the present state of biochemical knowledge has progressed to the point where serious attempts should be made to construct chemical models of living molecules. Most of the discussion of the origin of life has centered on the general energetic aspects and on the source of moderately complex organic molecules which would furnish raw material for chemical evolution. We believed that this problem has been solved, in principle, along the lines of Oparin's (1936, 1957) arguments. According to these, the action of solar radiation on the primitive atmosphere initiates a serious of condensations leading to the spontaneous formation of organic molecules. In addition, the very condensation of atomically dispersed cosmic matter which is the starting point of galactic, stellar and planetary evolution should lead to the synthesis of H-C-O-N- ... . polymers as the most prevalent state of all matter which has reached molecular dimensions (as ~~surrounded~~ summarized by Lederberg and Cowie, 1958). The scope of such synthesis will be locally limited by such factors as atomic concentrations, radiation and temperature intensities, the overabundance of hydrogen atoms, gravitational fractionation, and so forth. However, we suggest that any general formulation of biopoiesis can take for granted an unlimited variety of monomeric precursors, suitably activated for further chemical reaction. Of course much further work is needed on this aspect of the problem to delineate what can have happened, in detail, in the evolution of the earth or another planet.

We face then the second problem : the organization of postulated monomers into a 'living molecule'. A solution of nucleotides will not spontaneously polymerize into a specific polymer; however, the recent work of Watson and Crick ( ) and of Kornberg (1958) allows a straightforward model of polynucleotide synthesis, whereby an ensemble of nucleotides activated as the triphosphates may be organized into a linear polymer with a specific sequence of nucleotides determined by the structure of a polynucleotide template present during the reaction. (1) But this synthesis requires, in addition to the nucleoside triphosphate precursors and polynucleotide template, a specific enzyme: polynucleotide phosphorylase. Since the biosynthesis of this enzyme is presumably governed by a specific polynucleotide, and it is in turn necessary for the replication of the same polynucleotide, we cannot believe that this system represents the primitive origin of biological replication; to do so, we would have to postulate the simultaneous, stochastic, non-enzymatic production both of the enzyme and of the corresponding polynucleotide. While the argument might be rescued in various ways, we believe that any simple model should depend on a non-enzymatic condensation in which the template is the only necessary specific macromolecule. In a word, the primitive genes would be capable of spontaneous replication in an environment richly endowed with activated precursors, more efficient catalysis by accessory enzymes being a later evolution.

At this point we face three possibilities: either nucleoside triphosphates are capable of a (presumably inefficient) spontaneous condensation, and therefore remain as candidates for the primitive elements, or they are also an evolutionary refinement from some simpler, more common of greater spontaneous reactivity.
(2) or their condensation can be mediated by a non-enzymatic catalyst (silica; clay...) or (3)...

These hypotheses are accessible to experimental study, but have not yet been extensively attacked. Spontaneous condensation might be too slow for convenient laboratory study, and still quite rapid

enough to meet evolutionary requirements. (there is already some evidence for nucleotide condensation on chromatographic columns.) The third possibility warrants study not only as a model for the terrestrial evolution of life, but in its own right as a way of approaching the question of the uniqueness of the basis of life in DNA. The ubiquity of DNA in contemporary organisms, it should be said, is a powerful but not altogether conclusive argument against the third proposition.

What are the requirements of our model? To put it in its simplest form we should look for two monomers A and B which can readily condense under specified conditions. The four possible dimers, A-A, A-B, B-A, and B-B should be energetically nearly equivalent so that the proportion of potential products will be relatively uninfluenced by thermodynamic considerations. The dimers should be capable of further condensation with monomers in much the same fashion. These criteria are so far commonplace in polymer chemistry. What we now seek is a system which, like DNA, permits a second class of interaction between the monomers, some form of weak bonding (hydrogen bonding; van der Waals, or whatever) so that an existing polymeric sequence can orient the choice of the next condensing unit. This would also suppose a rather high degree of association among the polymers themselves, namely an approach to crystallinity. The accompanying diagram will illustrate the contemplated process, and it is of course closely analogous to the specific models of DNA synthesis.

How can we screen potential monomers? The second order forces are believed to be comparable to those involved in crystallization; the free energy of crystallization of the monomers can therefore give one clue. Another would be evidence of a high incidence of weakly bound dimers in solution, and especially of paracrystalline associations of the pure polymers. Again by analogy with DNA, there are two modes of orientation: identical and complementary. Complementary monomers should display a high free energy of mixed crystallization. These features are not necessarily apparent in nucleotides, as the function of the enzyme may be, in part, to stabilize an optimum configuration. Finally, as with DNA, scale models of potential elements may help in the choice.

But this is only a hastily contrived list. We believe that the theoretical problem of designing the specifications warrants careful study before we attempt to apply the specifications to the choice of promising candidates, and finally to the design of experimental tests. These tests would also include a consideration of hypothesis 3.1 and 3.2. We would hope that a year's preliminary theoretical work on each of the preliminary steps would be warranted; it might be possible meanwhile to start some of the experimentation for 3.1 and 3.2. On this basis, a two year's investment in time, effort and money should tell us whether this approach is premature. It seems a small one to us, discounting the limited probability of success, in relation to the magnitude of the problem.

What would be the tangible result of a successful conclusion? It would be the description of a poplymer (A, B)^n and its precursors Ax and Bx which could undergo a condensation say as follows:

ABBAABABBAAAB + 7 Ax + 6 Bx --> 2 ABBAABABBAAAB + 17x...

at least measurably more often in the presence of ABBAABABBAAAB than in its absence. (This may well sound like abracadabra!) Certainly, other things being equal, one basis of choice would be the ease of analysis of the polymer. A sequence analysis would be desirable but not essential, as the gross composition (say 7A & 6B) if found to be dependent on that of the primer and independent of the input

monomers would be sufficient preliminary evidence.

This would not be a living organism in any customary sense, but it would be a large step in achieving a chemical model of one. The next step would presumably be to (a) define further the conditions needed for more exact replication, and (b) to search for some catalytic activity of some polymers. If some polymeric configurations were able to accelerate some reaction such as

$$A + Cx = Ax + C$$

to increase the availability of component Ax we would be hard put to deny the system a place in our scheme of living things.

So nice a conclusion can hardly be hoped for, but even wholly unsuccessful attempts, particularly on the theoretical side, should help to sharpen our eventually attack on the problem.